https://doi.org/10.63181/ujcvs.2025.33(3).81-87
UDC 616.14+616-005.6-085

Dmytro A. Makivchuk, MD, PhD Fellow, Junior Research Associate, Scientific Department of Minimally Invasive Surgery, https://orcid.org/0000-0002-5894-6355

Yurii M. Hupalo, MD, PhD, vascular surgeon, Senior researcher at the department of minimally invasive surgery, https://orcid.org/0000-0002-4856-1398

State Institution of Science «Center of Innovative Healthcare Technologies» State Administrative Department, Kyiv, Ukraine

Comparative Analysis of the Treatment of Patients with Lower Limb Artery Thrombosis and Outflow Artery Injury Using Recombinant Tissue Plasminogen Activator as a Thrombolytic Agent

Abstract

Aim. To evaluate the effectiveness of recombinant tissue plasminogen activator (rtPA) in the treatment of patients with lower limb arterial thrombosis and outflow artery injury, and to conduct a comparative analysis of treatment following catheter-directed thrombolysis (CDT).

Materials and Methods. The study analyzed the treatment outcomes of 64 patients who underwent CDT using rtPA. During the postoperative period and at the outpatient stage of treatment, patients received anticoagulant therapy according to the VOYAGER PAD protocol and underwent regular duplex ultrasound (DUS) vascular monitoring.

Results. Most patients demonstrated marked regression of ischemia, reduction of pain syndrome, and absence of critical hemorrhagic complications. Limb preservation was achieved in 93.3 % of patients within 2 months after CDT. The use of CDT allowed achieving a high rate of revascularization and reduced the risk of recurrent thrombosis.

Conclusions. Recombinant tissue plasminogen activator (rtPA) is an effective thrombolytic agent for CDT in the treatment of patients with acute lower limb arterial thrombosis (ALLAT) and concomitant outflow artery injury. The results of this study suggest that endovascular methods with additional angiographic control of distal blood flow are a recommended treatment option for patients with ALLAT and run-off arterial lesions. These methods demonstrated a high success rate in revascularizing the affected arteries and improving the degree of lower-limb ischemia, as evidenced by regression according to the Rutherford classification. The combination of CDT with secondary angioplasty proved beneficial in certain patients with hemodynamically significant steno-occlusions that may have contributed to run-off arterial thrombosis.

Keywords: *limb survival, anticoagulant therapy. myocardial infarction (MI), arterial hypertension, revascularization.*

Introduction. Acute lower limb ischemia (ALLI) is a pathological condition that occurs as a result of a sudden disruption of tissue perfusion, commonly caused by thrombosis or arterial embolism. ALLI is characterized by rapid onset and progression to critical ischemia, posing a significant risk of limb loss if timely treatment is not undertaken.

Particular clinical importance is associated with lesions of the outflow arteries, such as thrombotic occlusion of the popliteal and tibioperoneal arterial segments. In such cases, symptoms may be more isolated and pronounced, and collateral compensation is insufficient. Consequently, when restoring proximal blood flow, incomplete distal revascularization can result in rethrombosis of the reconstructed segment and irreversible necrotic changes in the limb. The threat to limb viability affects overall survival, particularly in patients with comorbidities. Without proper treatment, ALLI can progress within the first two weeks [1,2], with mortality among such patients reaching 15-20 %. High mortality is linked not only to ischemic limb damage, but also to severe concomitant pathologies, in particular cardiovascular and cerebrovascular diseases, as well as reperfusion tissue injury.

Catheter-directed thrombolysis (CDT) is one of the methods for treating patients with ALLI caused by acute lower limb arterial thrombosis (ALLAT). According to the literature [3], CDT is an effective method that reduces both amputation and mortality rates. CDT can be performed using various thrombolytic agents, including

streptokinase, urokinase, and recombinant tissue plasminogen activator (rtPA).

However, in Ukraine, only alteplase (rtPA) is currently available, and its use is subject to certain limitations.

Therefore, the treatment of ALLI should include not only local thrombus removal but also a comprehensive systemic approach aimed at correcting hemodynamic disturbances, preventing thrombotic complications, and reducing the risk of recurrence [4].

Aim. The study aims to compare the efficacy of CDT with rtPA in patients with ALLI caused by ALLAT.

Materials and Methods. Between February 2020 and May 2025, 82 patients with ALLAT and outflow artery disease were examined. All patients reported the onset of symptoms within 0-14 days prior to examination. The cases were accompanied by clinical manifestations of ALLI, including pain at rest and during ambulation, pallor and swelling of the affected lower limb, and cyanosis of the foot and lower leg.

Exclusion criteria were: presence of ankle or knee contractures, a history of intracranial hemorrhage within the previous 2 months, recent open surgery (within the last 30 days), or an active source of bleeding. Patients with aneurysmal arterial lesions, including popliteal artery aneurysm thrombosis, and patients who underwent non-rtPA-based CDT were also excluded from the study.

A total of 64 patients with grades IIA–IIB ALLI, according to the Rutherford classification, were included in the study: grade II-A – 32 patients (50%) and grade II-B – 32 patients (50 %).

Among the patients, there were 20 female patients (31.2 %) and 44 male patients (68.8 %). The average age of the patients was 63 ± 11 years. Comorbidities were as follows: type II diabetes mellitus in 17 patients (26.6 %), arterial hypertension in 37 patients (57.8 %), atrial fibrillation in 16 patients (25 %), and rheumatic disease in 2 patients (3.1 %).

All patients underwent duplex ultrasound (DUS) of the lower limb arteries. According to DUS results, thrombotic occlusion involving the femoropopliteal and below-the-knee (BTK) arterial segments with associated run-off artery injury (absence of blood flow in the tibial and pedal arteries) was detected. Thrombotic occlusion of the BTK arterial segments with run-off arterial lesions was also diagnosed.

During hospitalization and treatment planning for ALLAT, a standard patient examination protocol was followed, which included performing DUS using Mindray M5 and Samsung Medison R3 ultrasound systems. To assess blood flow velocity and type, a linear ultrasound probe with a variable frequency range of 9–15 MHz was used. Diagnostic angiography and endovascular interventions were performed using the Philips Alura F920 angiographic system.

During diagnostic arteriography, the level of thrombotic occlusion, the presence and characteristics of collateral compensation, and the visualization of outflow arteries were determined. A 6F introducer was inserted according to the Seldinger method during angiography.

All patients underwent CDT after diagnostic arteriography and confirmation of ALLAT with run-off artery lesions.

In this study, recombinant tissue plasminogen activator (rtPA) was used for thrombolysis according to the following protocol: an initial bolus infusion of 10 mg intraprocedurally over the first 15 minutes, followed by continuous infusion of 10 mg/h for 4 hours. Additionally, heparin infusion was administered intraarterially at a rate of 1000 U/h for 12 hours. During bolus administration, patients' vital signs were monitored and standard anesthesia monitoring parameters were recorded.

During thrombolytic therapy and subsequent heparin infusion, the following procedures were performed: continuous monitoring of vital signs, along with assessment of hemostasis at the puncture site. Ultrasound evaluation was carried out to assess the presence and characteristics of blood flow in the run-off arteries, combined with clinical assessment every 30 minutes.

The study complied with the requirements of the Council of Europe Convention on Human Rights and Biomedicine, the World Medical Association Declaration of Helsinki on the ethical principles of medical research involving human subjects, and the current regulatory documents of the Ministry of Health of Ukraine. All patients provided informed voluntary consent to participate in the study. The study protocol was approved by the ethics committee.

Statistical analysis and data visualization were performed using IBM SPSS Statistics v.27.0 (Armonk, NY, USA), MedCalc v.23.3.4 (MedCalc Software Ltd., Belgium), EZR v.1.68, and RStudio v.2025.05.1+513 for R v.4.5.1. The frequency of qualitative nominal variables (absolute and relative [%]) in two independent samples was compared using the Fisher exact test. In more than two independent groups, if a statistically significant difference was observed according to the χ^2 test, pairwise comparisons of qualitative nominal variables were performed using the Fisher exact test with Bonferroni correction. Quantitative assessment of the clinical effect was conducted using the relative risk (RR) indicator, with 95 % confidence intervals (CI) calculated via the combined exact binomial test (melded binomial test). In related (dependent) samples, the frequency of qualitative nominal features was compared using McNemar's test. The severity of ALLI (Rutherford grade [an ordinal qualitative measure]) in related samples was compared using the Wilcoxon T-test. The results of the comparison included the difference in medians, determined by the Hodges-Lehmann method (ΔMeHL) with 95 % CI. For all statistical tests, the level of statistical significance was set at $p<0.05$ (with Bonferroni correction).

ALLAT with run-off artery lesions occurring in stenoocclusive diseases of the lower-limb arteries was diagnosed in 17 patients (48.6 %). Patients with ALLAT and run-off artery lesions due to thromboangiitis obliterans

numbered 4 (11.4 %). ALLAT with run-off artery lesions caused by thromboembolism was observed in 9 patients (25.7 %). Additionally, this study included 5 patients (14.3 %) with ALLAT and run-off artery lesions occurring during intraprocedural PTA.

Fifty-four patients (84.4 %) were hospitalized for the first time with ALLI, while 10 patients (15.6 %) were re-admitted. The distribution of ischemia severity according to the Rutherford classification was as follows: IIa – 34 patients (53.1 %) and IIb – 30 patients (46.9 %).

Results. Open surgical interventions (without additional intraoperative CT control) were performed in 17 patients (26.6 %), while endovascular interventions were performed in 47 patients (73.4 %).

Treatment outcomes were evaluated within 2 months, before the transition of ischemia to a chronic threatening stage. The analysis of endpoints included rethrombosis, occurrence of amputation, and limb preservation in the two intervention groups (Table 1).

Table 1

Comparative results of endovascular and open interventions

Endpoints	Endovascular interventions N=47	Open interventions N=17	p_2
Rethrombosis, n (%)	13 (27.7)	10 (58.8)	0.037
Amputation, n (%)	4 (8.5)	6 (35.3)	0.017
Limb preservation, n (%)	43 (91.5)	11 (64.7)	

In patients who underwent open surgical interventions without intraoperative angiographic control, the risk of rethrombosis was higher – RR of 2.127 (95 % CI 1.007-4.225) (p=0.048).

The risk of amputation in the open surgical intervention group, compared to endovascular, was – RR 4.147 (95 % CI 1.103-17.672) (p=0.034).

Among the endovascular interventions, 43 procedures were CDT or CDT supplemented with using rtPA. The results were analyzed according the subgroup of patients who underwent CDT (Figure 1).

CDT was performed as a monomethod in 17 patients (26.6 %), CDT supplemented with percutaneous transluminal angioplasty (PTA) in 17 patients (26.6 %) and thrombotic mass canalization (balloon predilatation of the thromboocclusive site) combined with CDT in 9 patients (14 %), additionally, in 5 (7.8 %) cases thrombosis with run-off arteries lesion occurred intraprocedural during PTA.

An analysis of the surgical techniques used and the respective combinations of CDT was performed (Figure 2).

When comparing the frequency of rethrombosis, it was found that patients who underwent CDT followed by additional PTA of causal stenoses and occlusions, had a lower level of the following rethrombosis (Table 2).

In patients who underwent thrombotic mass canalization (PTA of thromboocclusive sites) combined with CDT, no significant reduction in the rate of rethrombosis was observed (Table 3).

Analysis of amputations frequency in the CDT group supplemented with PTA showed a statistically non-significant trend towards a reduced risk (Table 4).

However, in the group undergoing thrombotic mass drainage supplemented with CDT, no statistically significant difference was observed compared with the other intervention groups (Table 5).

Data on the dynamics of the ALLI severity in 42 patients who underwent CDT are presented in Figure 3.

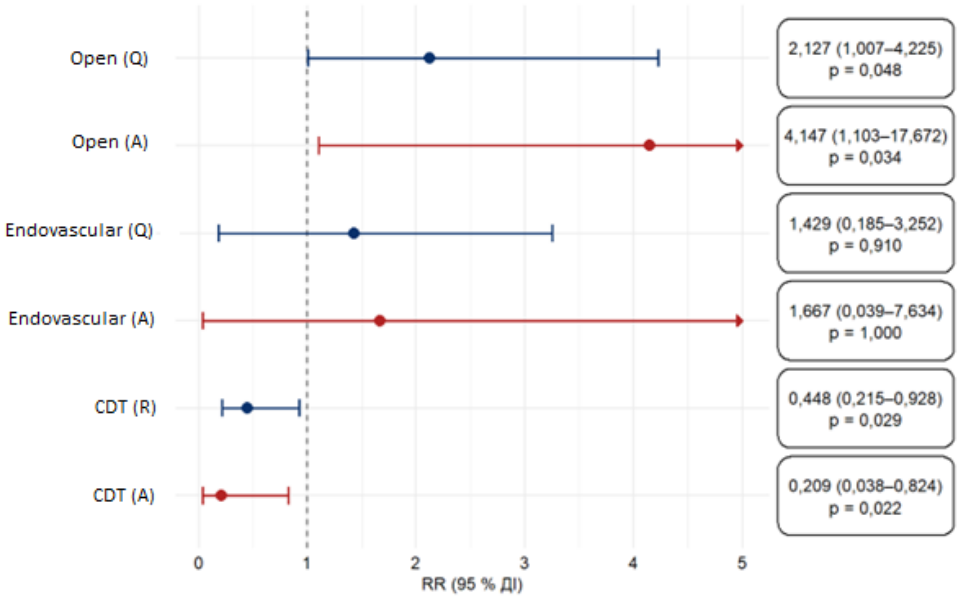

Figure 1. *Risk ratio Forest graph of open, endovascular interventions and CDT*

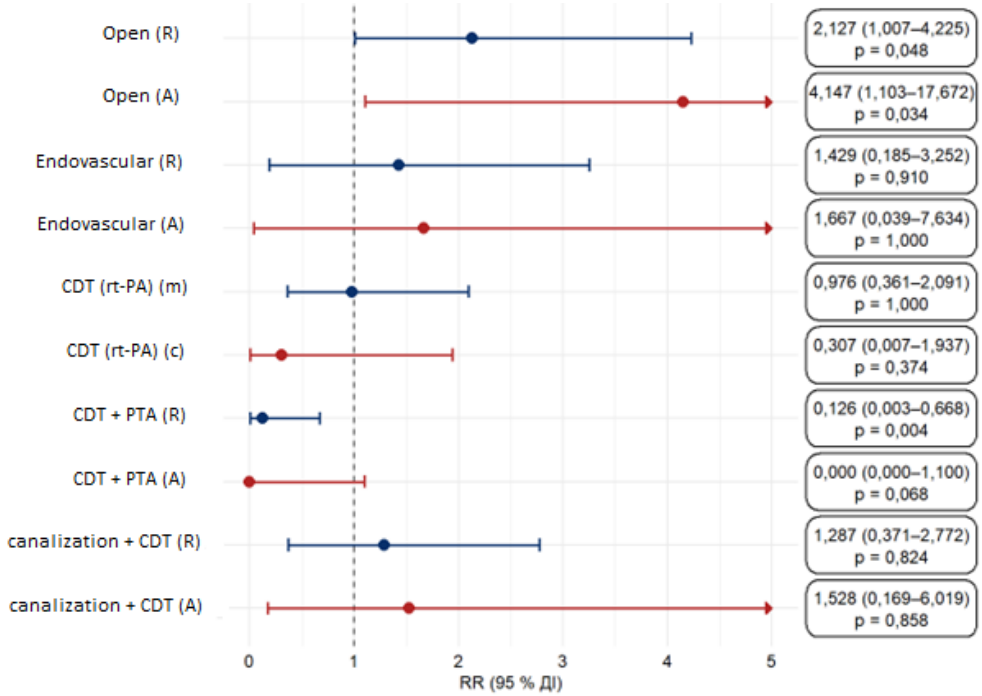

Figure 2. *Risk ratio Forest graph of open, endovascular interventions, CDT, CDT combined with PTA, thrombotic mass canalization combined with CDT*

Table 2

CDT combined with PTA rethrombosis risk ratio compared other interventions

Indicators	Other interventions N=47	CDT+PTA N=17	p_2	RR (95 % ДІ)	p_3
Rethrombosis N`=23	22	1	0.003	0.126 (0.003-0.668)	0.004
Segment functioning N`=41	25	16			

Table 3

Thrombotic mass canalization combined with CDT rethrombosis risk ratio compared other interventions

Indicators	Other interventions N=55	Canalization + CDT N=9	p_2	RR (95 % ДІ)	p_3
Rethrombosis N`=23	19	4	0,711	1,287 (0,371-2,772)	0,824
Segment functioning N`=41	36	5			

Table 4

CDT combined with PTA amputation risk ratio compared to other interventions

Indicators	Other interventions N=47	CDT+PTA N=17	p_2	RR (95 % ДІ)	p_3
Amputation N`=10	10	0	0.051	0 (0-1.100)	0.068
Limb preservation N`=54	37	17			

Table 5

Thrombotic mass canalization combined with CDT amputation risk ratio compared other interventions

Indicators	Other interventions N=55	Canalization + CDT N=9	p_2	RR (95 % ДІ)	p_3
Amputation N`=10	8	2	0.622	1.528 (0.169-6.019)	0.858
Limb preservation N`=54	47	7			

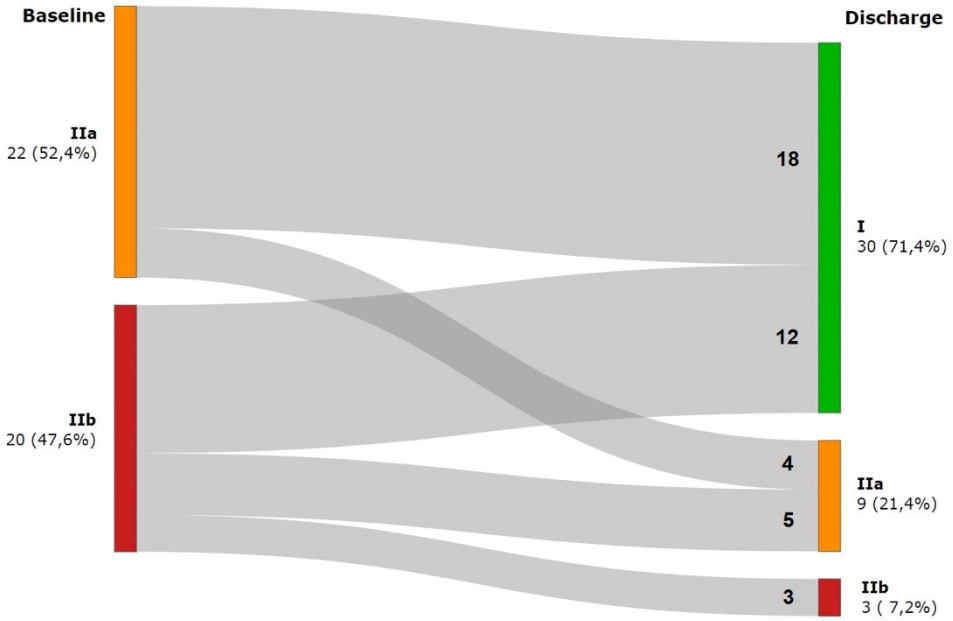

Figure 3. *Dynamics of ALLI severity from baseline to discharge (Sankey diagram)*

The nodes represent the absolute number (n) and relative proportion (%) of patients with the corresponding Rutherford class at baseline and at discharge. The thickness of the "flows" corresponds to the number of patients transitioning between severity classes during treatment, with annotations indicating the corresponding "flow".

In the post-procedural period, the frequency of patients in Rutherford class IIa decreased from 52.4 % at baseline to 21.4 % (p=0.011), and in class IIb from 47.6 % to 7.2 % (p<0.001), with transitions to class I observed in 18 and 12 cases, respectively. Overall, 30 patients (71.4 %) had symptoms corresponding to Rutherford class I at the end of the inpatient period.

In general, treatment was associated with regression of ALLI by, on average, one Rutherford class (ΔMeHL: -1 [95% CI: -1.5...-1]; p<0.001), observed in more than half of the cases (n=23 [54.8 %]). At the same time, in 12 patients (28.6 %), a more pronounced improvement was noted, with a decrease in the severity of clinical manifestations by two Rutherford classes compared to the initial state (transition from class IIb to I). In 7 cases (16.7 %), no clinically significant transition was observed at discharge, indicating either ineffectiveness of the revascularization performed or the occurrence of rethrombosis.

Discussion. The results demonstrated promising outcomes, with a high rate of successful revascularization and regression of ALI. Most patients experienced an improvement of one to two stages according to the Rutherford classification, indicating a favourable response to the CDT intervention.

The CDT procedure was performed using rtPA as the thrombolytic agent, administered via a volumetric infusion pump. Most patients reported reduced pain, and no major bleeding complications occurred during the procedure, indicating that CDT is both safe and effective for restoring blood flow in patients with ALI.

Despite the high overall success rate of CDT, this case emphasizes the need for careful patient selection and ongoing monitoring to identify patients who may require alternative treatment approaches.

In some cases, follow-up arteriography and angioplasty were performed to address steno-occlusive lesions, further improving the outcomes of the intervention. This combination of CDT with secondary angioplasty demonstrated superior results compared with intraoperative intraarterial thrombolysis [5,6].

Long-term outcomes in the CDT patient group were relatively favourable, particularly for patients undergoing secondary angioplasty, compared with those receiving CDT alone in the short term [7,8,9].

Due to the catheter-directed scheme of thrombolytic therapy at the indicated severity, no critical haemorrhagic complications were observed. Other studies of CDT similarly report a low risk of major bleeding events [10–15].

Conclusions

1. The results of this study suggest that endovascular methods with additional angiographic control of distal blood flow are a recommended treatment option for patients with ALLAT and run-off arterial lesions. These methods demonstrated a high success rate in revascularizing the affected arteries and improving the degree of lower-limb ischemia, as evidenced by regression according to the Rutherford classification.
2. The combination of CDT with secondary angioplasty proved beneficial in certain patients with hemodynamically significant steno-occlusions that may have contributed to run-off arterial thrombosis.

3. Long-term follow-up and anticoagulant therapy were crucial in maintaining the efficacy of CDT and preventing recurrent thrombosis in most patients.

In summary, CDT is a valuable and effective treatment option for patients with acute lower limb arterial thrombosis and ALI, offering the potential for successful revascularization and improved clinical outcomes.

Список використаної літератури
References

1. Luan TMB, Bang HT, Tan NM, et al. Catheter-directed intra-arterial thrombolysis in the treatment of acute thrombosis of below-the-knee arteries. Radiol Case Rep. 2021;16(8):2086–90. Available from: https://doi.org/10.1016/j.radcr.2021.05.012
2. Ahmed A, Naeem N, Jain A, Arora S, Elgendy IY. Acute Limb Ischemia Interventions. Interv Cardiol Clin. 2025;14(2):273–82. Available from: https://doi.org/10.1016/j.iccl.2024.11.012
3. Theodoridis PG, Davos CH, Dodos I, et al. Thrombolysis in acute lower limb ischemia: Review of the current literature. Ann Vasc Surg. 2018;52:255–62. Available from: https://doi.org/10.1016/j.avsg.2018.02.030
4. Norgren L, Hiatt WR, Dormandy JA, et al. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). J Vasc Surg. 2007;45(Suppl S):S5–67. Available from: https://doi.org/10.1016/j.jvs.2006.12.037
5. Hiatt WR, Bonaca MP, Patel MR, et al. Rivaroxaban and aspirin in peripheral artery disease lower extremity revascularization: Impact of concomitant clopidogrel on efficacy and safety. Circulation. 2020;142(23):2219–30. Available from: https://doi.org/10.1161/CIRCULATIONAHA.120.050465
6. Dragas M, Zlatanovic P, Koncar I, et al. Effect of intra-operative intra-arterial thrombolysis on long term clinical outcomes in patients with acute popliteal artery aneurysm thrombosis. Eur J Vasc Endovasc Surg. 2020;59(2):255–64. Available from: https://doi.org/10.1016/j.ejvs.2019.10.013
7. Hupalo YM, Makivchuk DA. Catheter directed thrombolysis in acute limb ischemia patients: A single center's experience. Wiad Lek. 2023;76(10):2156–60. Available from: https://doi.org/10.36740/WLek202310104
8. Cheng SC, Wang Z, Cao XS, Zhang YZ, Wang XC, Han XQ. Clinical efficacy of simultaneous versus staged stent implantation after percutaneous mechanical thrombectomy in IVCS patients with acute IFDVT. Saudi Med J. 2025;46(7):836–40. Available from: https://doi.org/10.15537/smj.2025.46.7.20240859
9. Makivchuk DA, Hupalo YM, Didenko SM. Analysis of the outcomes of catheter-directed thrombolysis in patients with lower limb arterial thrombosis involving outflow arteries. Clin Prev Med. 2025;(3):76–83. Available from: https://doi.org/10.31612/2616-4868.3.2025.10
10. Zatykó DZ, Pomozi E, Pataki Á, Szeberin Z. Akut, kritikus alsó végtagi ischaemia kezelése katéteres thrombolysissel [Catheter-directed thrombolysis in acute critical limb ischemia]. Orv Hetil. 2022;163(11):424–30. Available from: https://doi.org/10.1556/650.2022.32376
11. Poorthuis MHF, Brand EC, Hazenberg CEVB, et al. Plasma fibrinogen level as a potential predictor of hemorrhagic complications after catheter-directed thrombolysis for peripheral arterial occlusions. J Vasc Surg. 2017;65(5):1519–26. Available from: https://doi.org/10.1016/j.jvs.2016.11.025
12. Johnson LD, Cole JC, Erdman MJ, Boppana LKT, Najjar N, Shald EA, et al. Safety and efficacy of thrombolytic interventions in the treatment of intermediate and high-risk pulmonary embolism. Blood Coagul Fibrinolysis. 2025;36(6):253–60. Available from: https://doi.org/10.1097/MBC.0000000000001375
13. Lakhter V, Bichard C, Ouriel K, Firth B, Rali P, Bashir R. Safety and Feasibility of On-the-Table Pharmacomechanical Lysis for Acute Intermediate-Risk Pulmonary Embolism: The RESCUE-II Study. JACC Adv. 2025;4(6 Pt 1):101789. Available from: https://doi.org/10.1016/j.jacadv.2025.101789
14. Tao M, Zhang XH, Yan LW, Mo DC, He RX, Wang T, et al. Risk of intracerebral haemorrhage with tenecteplase versus alteplase in acute ischaemic stroke: a meta-analysis. J Neurol. 2025;272(5):334. Available from: https://doi.org/10.1007/s00415-025-13081-5
15. Xie G, Jiang G, Huang L, Sun S, Li X, Wu B, et al. Asparagine Endopeptidase Inhibition Attenuates Tissue Plasminogen Activator-Induced Brain Hemorrhagic Transformation After Ischemic Stroke. CNS Neurosci Ther. 2025;31(3):e70345. Available from: https://doi.org/10.1111/cns.70345

Порівняльний аналіз лікування пацієнтів із тромбозом артерій нижньої кінцівки з ураженням артерій відтоку, із використанням рекомбінантого активатора тканинного плазміногену як тромболітичного агента

Маківчук Д. А., Гупало Ю. М.

Державна наукова установа «Центр інноваційних технологій охорони здоров'я» Державного управління справами, м. Київ, Україна

Резюме

Мета. Оцінити ефективність рекомбінантного тканинного активатора плазміногену (rtPA) у лікуванні пацієнтів з тромбозом артерій нижніх кінцівок та ураженням артерій відтоку, а також провести порівняльний аналіз лікування після катетер-спрямованої тромболітичної терапії (КСТТ).

Матеріали та методи. У дослідженні проаналізовано результати лікування 64 пацієнтів, яким було проведено КСТТ із застосуванням rtPA. У післяопераційний період та на амбулаторному етапі пацієнти отримували антикоагулянтну терапію згідно з протоколом VOYAGER PAD та проходили регулярний дуплексний ультразвуковий сканування (УЗДС) для судинного моніторингу.

Результати. У більшості пацієнтів спостерігалася значна регресія ішемії, зменшення больового синдрому та відсутність критичних геморагічних ускладнень. Збереження кінцівки було досягнуто у 93,3% пацієнтів протягом 2 місяців після КСТТ. Використання КСТТ дозволило досягти високої частоти реваскуляризації та знизити ризик повторного тромбозу.

Висновки. Рекомбінантний тканинний активатор плазміногену (rtPA) є ефективним тромболітичним засобом для КСТТ при лікуванні пацієнтів з гострим тромбозом артерій нижніх кінцівок (ТАНК) та ураженням артерій відтоку. Результати дослідження свідчать, що ендоваскулярні методи з додатковим ангіографічним контролем дистального кровотоку є рекомендованим варіантом лікування пацієнтів із ТАНК та ураженням артерій відтоку. Ці методи продемонстрували високий рівень успішної реваскуляризації уражених артерій та зниження ступеня ішемії нижніх кінцівок, що підтверджується регресією за класифікацією Рутерфорда. Поєднання КСТТ із вторинною ангіопластикою виявилося корисним у деяких пацієнтів із гемодинамічно значущими стенозами або оклюзіями, які могли спричиняти висхідний тромбоз.

Ключові слова: *збереження кінцівки, антикоагулянтна терапія, інфаркт міокарда (ІМ), артеріальна гіпертензія, реваскуляризація.*

Стаття надійшла в редакцію / Received: 01.08.2025
Після доопрацювання / Revised: 01.09 2025
Прийнято до друку / Accepted: 03.09.2025